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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,450	09/01/2005	Marc Donath	4614-0160PUS1	5584

2292 7590 11/02/2007
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EXAMINER	
DANG, IAN D	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
11/02/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/517,450	DONATH, MARC	
	Examiner	Art Unit	
	Ian Dang	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Exhibit A*.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 20 August 2007 has been entered in full. Claims 1-14 have been cancelled and claims 15-21 have been added.

Claims 15-21 are pending and under examination.

Rejection Withdrawn

35 USC § 112, Second paragraph, and 35 USC § 101

Applicant's response and cancellation of claims 1-14 filed on 08/2/2007 have overcome the rejection of claims 1-7 under 35 U.S.C. § 112, Second paragraph, and 35 U.S.C. § 101. The rejection of claims 1-7 under 35 U.S.C. § 112, Second paragraph, and 35 U.S.C. § 101 has been withdrawn.

Claim Rejections - 35 USC § 112 (New Matter)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a new matter rejection. The amended claim represents a departure from originally filed. Although Applicant has pointed out the location for the support for the amended claims in the specification, the examiner has determined that the support is not sufficient. The amended claims 17 and 20 recite "Dose of 0.1 to 1000mg of anakinra per kg of body weight", and the amended claim 21 recites "Dose of 0.1 to 1000mg of PDTC per kg or body weight". However, the specification does not specifically teach that recited ranges for anakinra and PDTC.

Claim Rejections - 35 USC § 112 (Written Description)

Although Applicant's response and cancellation of claims 1-14 filed on 08/2/2007 have overcome the rejection of claims 1-14 under 35 U.S.C. § 112, First paragraph (Written Description), the addition of the claims 15-21 have raised new issues under 35 U.S.C. § 112, First Paragraph (Written Description).

In the response filed 08/20/2007, claims 1-14 drawn to the use of an interleukin 1 receptor antagonist for the preparation of a medicament for the treatment or prophylaxis of type 2 diabetes in a mammal filed 12/09/2004 have been cancelled and claims 15-21 drawn to a method comprising administering to a mammal in need of a medicament comprising a sufficient amount of anakinra have been newly added.

At page 4 of the response, Applicant argues that the substitution of the original claims with the new claims 15-21 renders moot the Examiner's written description rejection.

Applicant's arguments have been fully considered but are not found persuasive. To provide adequate written description and evidence of possession of claimed genus, the specification must provide efficient distinguishing identifying characteristics of the genus. The

factors to be considered include disclosure of complete or partial structure/function correlation, and other identifying characteristics. Accordingly, in the absence of sufficient recitation of distinguishing structural/physical and identifying characteristics, the specification does not provide adequate written description of the claimed genus.

The instant claims15-21 are drawn to a method of treating type 2 diabetes by administering a medicament comprising anakinra, but it does not disclose any identifying structural characteristics of anakinra. The specification defines anakinra as a polypeptide comprising 153 amino acids having the biological activity of the human interleukin 1 receptor antagonist (HIL-1Ra). While the specification discloses such general characteristics of anakinra (page 12), it fails to provide any specific identifying characteristics, such as the specific sequence of said 153 amino acids, so that one skilled in the art can correlate the anakinra encompassed by the claims as having a distinct structure. At page 12, the specification teaches that anakinra is Kineret® which is a recombinant, nonglycosylated form of the human interleukin 1 receptor antagonist (hIL-1Ra). Furthermore, the specification recites that Kineret® differs from native human IL-1Ra in that it has the addition of a single methionine residue at its N-terminal end. Kineret® consists of 153 amino acids and has a molecular weight of 17.3 kilodaltons (page 12, lines 48). However, at page 12 the specification does not provide specific structure, such that one skill in the art can identify the claimed anakinra used for treating type 2 diabetes of the instant application.

In addition, the disclosure of anakinra in the specification encompasses a broad genus of analogs, mutants, and variants of a 153 amino acid sequence, but the specification does not recite any specific identifying structural characteristics like the specific manner in which the 153 amino acids are arranged in the polypeptide correlating with distinct biological function for the claimed human interleukin 1 receptor antagonist. The specification does not provide any

disclosure regarding the number of amino acid changes, the identities of the amino acids and the location of these changes for the claimed anakinra analogs, mutants, and variants, while still retaining a biological function.

Claim Rejections - 35 USC § 112 (enablement)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) restoring glucose-stimulated insulin secretion in β islet cells exposed to high glucose in vitro by culturing the cells with IL-1Ra and PDTC (figure 6, page 6), (2) measuring the expression of IL-1Ra in human islets and observing its down regulation in human islets from patients with type 2 diabetes (figure 7, page 6), and (3) inhibiting β islet cell apoptosis and restoring β islet cell function in vitro comprising culturing the cells with IL-1Ra (figure 9, page 7; page 35-36), does not reasonably provide enablement for a method of treating or prophylactically suppressing type 2 diabetes, the method comprising administering to a mammal in need thereof a medicament comprising a sufficient amount of anakinra. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims. The basis of this rejection is set forth for claims 1-14 at pages 5-10 of the previous Office action of 10 April 2007.

In the response filed 08/20/2007, claims 1-14 drawn to the use of an interleukin 1 receptor antagonist for the preparation of a medicament for the treatment or prophylaxis of type

2 diabetes in a mammal filed 12/09/2004 have been cancelled and claims 15-21 drawn to a method comprising administering to a mammal in need of a medicament comprising a sufficient amount of anakinra have been newly added.

The rejection is maintained. Applicant's response and arguments filed on 08/20/2007 have been fully considered but they are not persuasive.

At page 5 of the response, Applicant argues that the enablement rejection has also been rendered moot because the current claims are directed to administration of the product "anakinra". In addition, Applicant alleges it is not necessary for compliance with the enablement requirement for the Specification to contain either a working example or results of clinical tests and the present specification describes prophetic examples at pages 21-28 and describes *in-vitro* test results at pages 28-37.

Applicant's arguments have been fully considered but are not found persuasive. Although Applicant need not actually have reduced the invention to practice prior to filing the application, the lack of a working example is only one factor to be considered, especially in a case involving an unpredictable art (MPEP § 2164.02). It is noted that the fact pattern of the case cited by the Applicant (*In re Borkowski*) and the fact pattern of the instant rejection are significantly different, and the court decision is not binding with regard to the instant rejection. For example, in *Borkowski*, the claims are drawn to a process for producing oxygenated hydrocarbons. The Court of Customs and Patent Appeals indicated that the specification need not contain a working example if one skilled in the art could practice it without undue experimentation and considering the nature of the claimed invention (process for producing hydrocarbons), the few hours of experimentation required were not an undue amount of time.

However, the case cited by Applicant does not have claims directed to a method of treatment comprising administering to a mammal a medicament comprising a sufficient amount of ankinra based on a result obtained in an *in vitro* experiment. Although Applicant is not required to provide examples of all embodiments of a claimed invention, Applicants must provide sufficient supporting evidence for the claimed invention. The presence of a working example is one factor among the 8 Wands factors necessary to fulfill the enablement requirement. However, with limited guidance and working examples in conjunction with consideration of the other 7 factors, Applicants have not provided sufficient evidence to make and use the claimed invention. The disclosure of the instant specification does not provide sufficient guidance to make/use the invention without undue experimentation.

Although Applicant is enabled for (1) restoring glucose-stimulated insulin secretion in β islet cells exposed to high glucose in vitro by culturing the cells with IL-1Ra and PDTC (figure 6, page 6), (2) measuring the expression of IL-1Ra in human islets and observing its down regulation in human islets from patients with type 2 diabetes (figure 7, page 6), and (3) inhibiting β islet cell apoptosis and restoring β islet cell function in vitro comprising culturing the cells with IL-1Ra (figure 9, page 7; page 35-36), Applicant is not enabled for a method of treating or prophylactically suppressing type 2 diabetes comprising administering to a mammal in need of a medicament comprising a sufficient amount of anakinra. Applicant has not satisfied the enablement requirement because Applicant is not enabled for (1) a medicament comprising anakinra and (2) an *in vivo* method of treating or prophylactically suppressing type 2 diabetes.

(1). Applicant is not enabled for a medicament comprising anakinra because the disclosure of anakinra in the specification does not disclose any identifying structural characteristics of

anakinra and encompasses a broad genus of analogs, mutants, and variants of a 153 amino acid sequence. The specification fails to provide any specific identifying characteristics, such as the specific sequence of said 153 amino acids, so that one skilled in the art can correlate the anakinra encompassed by the claims as having a distinct structure. In addition, the specification does not provide any disclosure regarding the number of amino acid changes, the identities of the amino acids and the location of these changes for the claimed anakinra analogs, mutants, and variants, while still retaining a biological function. Moreover, the specification does not recite any specific identifying structural characteristics like the specific manner in which the 153 amino acids are arranged in the polypeptide correlating with distinct biological function for the claimed human interleukin 1 receptor antagonist. Thus the specification does not enable any person skilled in the art to make/use the claimed anakinra in a medicament used for treating or prophylactically suppressing type 2 diabetes.

(2). Applicant is not enabled for an *in vivo* method of treating or prophylactically suppressing type 2 diabetes because the specification does not teach how to use anakinra or anakinra with pyrrolidinedithiocarbonate (PDTC) in a medicament without undue experimentation for the treatment of a disease in an animal. The specification indicates the treatment of diabetes (pg 11, line 10), but there are no working examples directed to a particular disorder in an animal or administration of anakinra or anakinra with PDTC to an animal for treatment of type 2 diabetes.

In addition, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope because of the large quantity of experimentation necessary to determine the quantity of anakinra or anakinra and PDTC to be administered, the duration of the treatment, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the

complex nature of the invention, and the unpredictability of the effects of anakinra or anakinra and PDTC *in vivo*.

Furthermore, Applicant is not enabled for an *in vivo* method of treating or prophylactically suppressing type 2 diabetes because several references authored by the inventor of the instant application recite that the *in vitro* model disclosed in the instant application and the therapeutic potential of treating islet inflammation in type 2 diabetes with a therapeutic are not enabled. For instance, the reference by Donath et al., (2005, Diabetes, Volume 54, Supplement 2, pages S108-S113) indicates that the findings that glucose induces of β-cell apoptosis can be done *in vivo* but these findings cannot reliably be replicated an *in vitro* setting (page S108, right column 2nd paragraph). Donath et al., (2005) teach that striking variations observed in the response of β-cell apoptosis caused by glucose in the *in vitro* studies can be explained by the limitations of the cell lines and rodent and human islets used these studies (page S109, left column, top paragraph). Donath et al. further indicate that these variations are caused by genetic background of the cells (page S109, left column, top paragraph).

Finally, another reference by Donath et al. (2003, cited in the IDS on the last page mailed 08/22/2005) teaches that based on current thinking, modulation of the intra-islet inflammatory mediators in type 1 and 2 diabetes appears as promising approach(page 466, left column, middle of 2nd paragraph). Furthermore, Donath et al. teach that the progressive decline in functional β-cell mass observed in diabetic patients may thus be prevented and even reversed; however, it will take several years until drugs are available with the primary aim of preventing the inflammatory process of islets (page 466, left column, middle of 2nd paragraph). Thus the inventor indicates that therapeutic for the treatment of diabetes 2 with a threrapeutic such as anakinra is still under investigation and requires large amount experimentation.

It is noted that the term "prophylactically suppressing type 2 diabetes" has been interpreted by the Examiner as meaning that an activity will not occur, i.e. type 2 diabetes will not occur.

In view of these teachings in the art and the limited guidance provided in the specification, it would require undue experimentation for one of skill in the art to be able to for treat or prophylactically suppress type 2 diabetes, comprising administering to a mammal in need thereof a medicament comprising a sufficient amount of anakinra.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boone et al. (US Patent No. 6,294,170, filed August 07, 1998) in view of Thompson et al. (US Patent No. 6,159,460, filed August 18, 1994).

It has been determined that anakinra has the registry number 143090-92-0 and is disclosed in the US patent US 6,294,170 as SEQ ID NO:2 (see exhibit A).

Boone et al. teach that interleukin-1 mediated diseases includes diabetes (e.g., insulin diabetes) (column 1, line 61) and the administration of the IL-1 receptor antagonist of SEQ ID NO:2 (named anakinra of the instant application) (column 6, lines 17-19) can act as a natural inhibitor of interleukin-1 (column 7, lines 11-12). Boone et al. does not teach the parenteral

administration. Boone et al. do not teach parenteral administration of an IL-1 receptor antagonist and a dosage of 0.1-1000 mg/kg of patient weight.

Thompson et al. teach that the IL-1 receptor antagonist can be administered parenterally, such as intraarticular, subcutaneous, or intramuscular route (column 9, lines 52-54). Furthermore, Thompson et al. teach that the dosage for the treatment of the interleukin-1 mediated disease, such as inflammatory bowel disease (column 10, lines 6-8).

Combining the teachings of both the above references, it would be obvious for one skilled in the art to treat type 2 diabetes comprising administering an IL-1 receptor antagonist anakinra as taught by Boone et al. (US Patent No. 6,294,170, filed August 07, 1998) by modifying the treatment method with the parenteral administration as taught by Thompson et al. (US Patent No. 6,159,460, filed August 18, 1994). One of ordinary skill in the art at the time the invention was made would been motivated to do so because Boone et al. clearly teach that diabetes is one of the disease conditions mediated by IL-1 and administration of a IL-1 receptor antagonist such as anakinra can lead to inhibiting IL-1 and thus control diabetes. Although the references do not teach the dosage of 0.1-1000 mg/kg of IL-1 receptor antagonist, the dosage range claimed would be well within the skill of the ordinary artisan. One skilled in the art would have expected success because methods for treating IL-1 mediated diseases by administering the nature IL-1 receptor antagonist anakinra were available and practiced at the time the invention was made. Accordingly, the invention taken as a whole would have been prima facie obvious to one of ordinary skill in the art.

Conclusion

No claim is allowed.

Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ian Dang whose telephone number is (571) 272-5014. The examiner can normally be reached on Monday-Friday from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ian Dang
Patent Examiner
Art unit 1647
October 25, 2007

MANJUNATH N. RAO, PH.D.
PRIMARY EXAMINER
A.U. 1647

Supr.

Application 10/597,450

Exhibit A

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=> e anakinra/CN
E1            1     ANAKIN (HUMAN)/CN
E2            1     ANAKIN (MUS MUSCULUS)/CN
E3            1 --> ANAKINRA/CN
E4            1     ANAKROM SD/CN
E5            1     ANALA R/CN
E6            1     ANALAPE/CN
E7            1     ANALBEN/CN
E8            1     ANALBITE/CN
E9            1     ANALCIME/CN
E10           1     ANALCIME (NA(ALSI2O6).H2O)/CN
E11           1     ANALCIME, CALCIAN (ALSI2(NA0.33-0.8CA0.1-0.33)O6.H2O)/CN
E12           1     ANALCIME, CALCIUM (CA(ALSI2O6)2.2H2O)/CN

=> s E3;D
L1            1 ANAKINRA/CN


L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2007 ACS on STN
RN   143090-92-0  REGISTRY
ED   Entered STN:  21 Aug 1992
CN   Interleukin 1 receptor antagonist (human isoform x reduced),
     N2-L-methionyl- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   26-177-Interleukin 1 receptor antagonist [methionyl] (human)
CN   2: PN: US6159460 PAGE: 27/28 claimed sequence
CN   2: PN: US6294170 SEQID: 2 claimed protein
CN   4: PN: US6294170 SEQID: 4 unclaimed protein
CN   Anakinra
CN   Antril
CN   Interleukin 1 receptor antagonist (human clone pAMG21-IL-1ra)
CN   Interleukin 1 receptor antagonist (human precursor)
CN   Kinaret
CN   Kineret
CN   N2-L-Methionylinterleukin 1 receptor antagonist (humanisoform x reduced)
FS   PROTEIN SEQUENCE
MF   Unspecified
CI   MAN
SR   US Adopted Names Council (USAN)
LC   STN Files:   ADISINSIGHT, ADISNEWS, BIOSIS, CA, CAPLUS, CBNB, CHEMCATS,
       CIN, DDFU, DRUGU, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MRCK*,
       PATDPASPC, PHAR, PROMT, PROUSDDR, RTECS*, TOXCENTER, USAN, USPAT2,
       USPATFULL
         (*File contains numerically searchable property data)
     Other Sources:   WHO

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**
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